

Epileptic Seizure Prediction: An overview

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Abstract:

Epilepsy is a neurological disorder marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain. The sudden and seemingly unpredictable nature of seizures is one of the most compromising aspects of the disease epilepsy. Most epilepsy patients only spend a marginal part of their time actually having a seizure and show no clinical signs of their disease during the time between seizures, the so-called inter-ictal interval. But the constant fear of the next seizure and the feeling of helplessness associated with it often have a strong impact on the everyday life of a patient (Fisher et al. 2000). A method capable of reliably predicting the occurrence of seizures could significantly improve the quality of life for these patients and open new therapeutic possibilities. Apart from simple warning devices, fully automated closed-loop seizure prevention systems are conceivable. Treatment concepts could move from preventive strategies towards on demand therapy which resets brain dynamics and minimize the risk during epilepsy.

Key words: History of seizure Prediction, Epilepsy, Seizure, Type of Epileptic Seizure.

1. Introduction:

Epilepsy is a condition that affects 0.6-0.8% of the world population, rendering it the most common neurological disorder after stroke. It is characterized by recurrent unprovoked seizures, due to abnormal, excessive or synchronous neuronal activity in the brain and by a vast range of causes, triggering events, symptoms and brain locations where the seizures originate. In 25% of the affected population, seizures cannot be controlled by antiepileptic drugs or surgery. However, it has been suggested, that at least some types of seizures are predictable.

Seizures compromise the quality of life of patients with epilepsy to a great extent and may result in serious self-injuries from various causes. Epilepsy has been also associated with a sudden death rate that is at least 10 times of the same rate for the general population (sudden unexplained death in epilepsy - SUDEP). Therefore, the importance and usefulness of seizure prediction cannot be

overstated, as it would increase epileptic patients' autonomy, drastically reduce accidents and self-injuries related to epileptic seizures and, as a whole, improve the patients' quality of life dramatically.

Epilepsy is also associated with an increased risk of mortality. Death may be related to an underlying brain disease, such as a tumor or infection, seizures in dangerous circumstances, leading to life-threatening injuries. Epilepsy-related deaths in young adults in the UK, for example, are 3 times higher than standard age-related mortality rates. Very importantly, people with epilepsy are at least 10 times more probable to suffer sudden death (sudden unexplained death in epilepsy – SUDEP) compared to the general population, with probable causes including cardiac or respiratory arrest. Controlling seizures is considered to be the most important preventive measure against SUDEP; hence, seizure prediction would contribute in this direction. From the social point of view, people with epilepsy

experience problems in the areas of personal relationships and even sometimes legislation. For example, people with epilepsy were prevented from marrying in the United Kingdom or the U until recently, while they can only drive if they have been free of seizures for a year.

The socioeconomic burdens of epilepsy are obvious from the abovementioned facts. Therefore, epileptic seizure prediction will not only lead to the production of new scientific knowledge, but also to a vast improvement in the quality of life of the patients as well as a decrease in the related social and economic costs. Furthermore, the scientific outcomes of the prediction could be further used in portable, personalized monitoring systems i.e., portable EEG and ECG, which will take advantage of the recent advances in body sensor network and mobile communications technology. This would further improve the quality of life by decreasing the frequency of hospital admissions (by self-managing the seizures where possible and avoiding accidents and self injuries). [39]

2. History of Seizure Prediction

Seizure prediction has a long history, starting in the 1970s [1] with very small data sets looking only at pre-seizure (preictal) events minutes to seconds before seizures. It has progressed over the past almost 40 years up to current methods, which use mathematical to analyze continuous days of multiscale intracranial electroencephalogram (IEEG) recordings [2]. Seizure prediction research, most important, has given hope for new warning and therapeutic devices to the 25% of epilepsy patients who cannot be successfully treated with drugs or surgery [3] One of the most insidious aspects of seizures is their unpredictability. In this light, in the absence of completely controlling a patient's epilepsy, seizure prediction is an important aim of clinical management and treatment. From a broader view, seizure prediction research has also transformed the way we understand epilepsy and the basic mechanisms underlying seizure generation. Seizures were once viewed as isolated and abrupt events, but we now view them as processes that develop over time and space in epileptic networks. Thus, what started as a goal of predicting seizures

for clinical applications has expanded into a field dedicated to understanding seizure generation.

The study of seizure generation necessarily encompasses a large collaborative effort between mathematicians, engineers, physicists, clinicians, and neuroscientists. However, it also requires large volumes of clinical data, which has led to more specific collaborations between epilepsy centers. These partnerships have come about through The International Seizure Prediction Group (ISPG), which held its Third Collaborative Workshop on Seizure Prediction in Freiburg, Germany, in October 2007. This workshop, and its two predecessors, allowed various groups to share computational methods, data, and ideas, and to focus on basic research and its translation to clinical relevance.

Recent research has definitively advanced progress in these areas [4,5] Looking further ahead, for successful prediction devices to emerge, many technical questions will need to be resolved to design systems that not only warns the patient of a seizure but also intervenes to preempt it. For example, the intervention strategy (drug versus stimulation or other method), the clinical interface (sensors, classifiers, etc.), and the number and site of electrode placement are just a few of the problems under investigation that will need definitive solutions. With the advent of new brain sensors, stimulation technologies, and the availability of large data sets of continuous EEG recordings for collaborative research, our progress toward understanding seizure generation and preventing its occurrence is accelerating.

This section briefly describes some of the major studies in the field. After some *early work* on the predictability of seizures dating back to the 1970s (Viglione and Walsh 1975)[10], attempts to extract seizure precursors from surface EEG recordings of absence seizures were carried out by different groups using linear approaches such as pattern detection and spectral analysis (see Mormann et al. 2007)[11].

Following the advent of the theory of nonlinear dynamics in the 1980s, time series analysts became aware of seizure prediction as a potential field of application. These and later studies predominantly analyzed EEG signals from patients undergoing video-EEG monitoring, with

chronic electrodes implanted directly inside or on the surface of the brain to localize the seizure focus for possible surgical resection. During the 1990s several quantitative EEG studies reported *pre-ictal phenomena* using characterizing measures such as the largest Lyapunov exponent (Iasemidis et al. 1990)[12], the correlation density (Martinerie et al. 1998)[13] or a dynamical similarity index (Le Van Quyen et al. 1999, 2001)[14,15]. The common feature of these studies was that their focus of interest was entirely limited to the pre-ictal period and that they did not include an evaluation of control recordings from the seizure-free interval, so the specificity of the applied techniques was not assessed. Another group of *proof-of-principle studies* addressed the issue of specificity by comparing pre-ictal changes in dynamics to inter-ictal control recordings, although the reported findings remained on an anecdotal level (Mormann et al. 2000, Navarro et al. 2002, Chávez et al. 2003)[16,17,18].

In the first *controlled studies* comprising defined groups of patients with pre-ictal and inter-ictal control recordings, measures like the correlation dimension (Lehnertz and Elger 1998)[19], dynamical entrainment (Iasemidis et al. 2001)[20], accumulated signal energy (Litt et al. 2001)[21] simulated neuronal cell models (Schindler et al. 2002)[22], or phase synchronization Mormann et al. 2003)[23] were shown to be capable to distinguish short segments of inter-ictal data from pre-ictal data.

These studies were followed by a number of studies (mostly carried out on more extensive data bases) that found a substantially poorer predictive performance than expected from earlier reports for measures like the correlation dimension (Aschenbrenner-Scheibe et al. 2003)[24], the similarity index (Winter alder et al. 2003)[25], and accumulated energy (Maiwald et al. 2004)[26]. Furthermore a controversy evolved regarding both the reproducibility of earlier studies (De Clercq et al. 2003)[27] and the general suitability of nonlinear measures used to characterize EEG time series (McSharry et al. 2003, Lai et al. 2003)[28,29].

Around the turn of the millennium, when mass storage capacity became more widely available,

epilepsy centers were able to store the complete data acquired during pre-surgical monitoring without the necessity of selecting sample recordings. In 2005, several groups published a series of studies that were carried out on a set of five continuous multi-day recordings provided by different epilepsy centers for the First International Collaborative Workshop on Seizure Prediction (Lehnertz and Litt 2005)[30] held in 2002. The aim of this workshop was to have different groups test and compare their methods on a joint data set. Results from the different groups for the most part showed a poor performance of univariate measures (D'Alessandro et al. 2005, Esteller et al. 2005, Harrison et al. 2005, Jouny et al. 2005, Mormann et al. 2005)[31,32,33,34]. A better performance was reported for bi- and multi-variate measures (Mormann et al. 2005, Le Van Quyen et al. 2005, Iasemidis et al. 2005)[34,36]. The observed pre-ictal changes were found to be locally restricted to specific channels rather than occurring as a global phenomenon.

The first attempts to test seizure prediction algorithms in a *prospective study* design (D'Alessandro et al. 2005, Iasemidis et al. 2005, 2003)[31,35] yielded sensitivities and specificity rates that most epileptologists would consider unacceptable for clinical implementation. Whether the performance of the algorithms was at all better than random was not investigated. Although two recent studies (Chaovalitwongse et al. 2005, Sackellares et al. 2006)[37,38] attempted such a validation against a random predictor, they failed to carry out a proper statistical comparison.

Prior to the Third International Workshop on Seizure Prediction in 2007, the workshop organizers initiated a public competition, in which participants could download the first parts of three continuous long-term recordings from three different patients. After training their algorithms on this data and optimizing them individually for each patient, participants could then submit their algorithms to have them tested on the remaining parts of the data. The benchmark for winning the competition was merely to outperform chance level (i.e. to predict a percentage of seizures that was higher than the percentage of time under false

warning). None of the submitted algorithms passed this test, so the competition continues to be open to the public.

3. Epilepsy

Epilepsy is a common serious neurological condition where there is a tendency to have seizures that start in the brain [6]. It is the fourth most common neurological disorder and affects people of all ages. It is characterized by unpredictable seizures and can cause other health problems. Epilepsy is a spectrum condition with a wide range of seizure types and control varying from person-to-person. Epilepsy is a chronic disorder, the hallmark of which is recurrent, unprovoked seizures. Many people with epilepsy have more than one type of seizure and may have other symptoms of neurological problems as well. Sometimes EEG testing, clinical history, family history and outlook are similar among a group of people with epilepsy. In these situations, their condition can be defined as a specific epilepsy syndrome. The human brain is the source of human epilepsy. Although the symptoms of a seizure may affect any part of the body, the electrical events that produce the symptoms occur in the brain. The location of that event, how it spreads and how much of the brain is affected, and how long it lasts all have profound effects. These factors determine the character of a seizure and its impact on the individual. Having seizures and epilepsy also can affect one's safety, relationships, work, driving and so much more. How epilepsy is perceived or how people are treated (stigma) often is a bigger problem than the seizures [7]. Epilepsy is usually only diagnosed after a person has had more than one seizure.

4. Seizure

A seizure is a sudden surge of electrical activity in the brain. A seizure usually affects how a person appears or acts for a short time. During a seizure, the electrical activity is caused by complex chemical changes that occur in nerve cells. Brain cells either excite or inhibit (stop) other brain cells from sending messages. Usually there is a balance

of cells that excite and those that can stop these messages. However, when a seizure occurs, there may be too much or too little activity, causing an imbalance between exciting and stopping activity. The chemical changes can lead to surges of electrical activity that cause seizures. Many different things can occur during a seizure. Whatever the brain and body can do normally can also occur. Seizures are not a disease in themselves. Instead, they are a symptom of many different disorders that can affect the brain. Some seizures can hardly be noticed, while others are totally disabling. [8]

5. Epilepsy Seizure Types

Based on the type of behavior and brain activity, seizures are divided into two broad categories: generalized and partial (also called local or focal). Classifying the type of seizure helps doctors diagnose whether or not a patient has epilepsy.

Generalized seizures are produced by electrical impulses from throughout the entire brain; partial seizures are produced (at least initially) by electrical impulses in a relatively small part of the brain. The part of the brain generating the seizures is sometimes called the focus. The most common types of seizures are listed below:

Generalized Seizures (Produced by the entire brain)	Symptoms
1. "Grand Mal" or Generalized tonic-clonic	Unconsciousness, convulsions, muscle rigidity
2. Absence	Brief loss of consciousness
3. Myoclonic	Sporadic (isolated), jerking movements
4. Clonic	Repetitive, jerking movements

5. Tonic	Muscle stiffness, rigidity
6. Atonic	Loss of muscle tone

5.1 Generalized Seizures

There are six types of **generalized seizures**. The most common and dramatic, and therefore the most well known, is the generalized convulsion, also called the **grand-mal seizure**. In this type of seizure, the patient loses consciousness and usually collapses. The loss of consciousness is followed by generalized body stiffening (called the "tonic" phase of the seizure) for 30 to 60 seconds, then by violent jerking (the "clonic" phase) for 30 to 60 seconds, after which the patient goes into a deep sleep (the "postictal" or after-seizure phase). During grand-mal seizures, injuries and accidents may occur, such as tongue biting and urinary incontinence.

Absence seizures cause a short loss of consciousness (just a few seconds) with few or no symptoms. The patient, most often a child, typically interrupts an activity and stares blankly. These seizures begin and end abruptly and may occur several times a day. Patients are usually not aware that they are having a seizure, except that they may be aware of "losing time."

Myoclonic seizures consist of sporadic jerks, usually on both sides of the body. Patients sometimes describe the jerks as brief electrical shocks. When violent, these seizures may result in dropping or involuntarily throwing objects.

Clonic seizures are repetitive, rhythmic jerks that involve both sides of the body at the same time.

Tonic seizures are characterized by stiffening of the muscles.

Atonic seizures consist of a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall[4].

5.2 Partial Seizures

Partial Seizures (Produced by a small area of the brain)	Symptoms
1. Simple (awareness is retained) a. Simple Motor b. Simple Sensory c. Simple Psychological	a. Jerking, muscle rigidity, spasms, head-turning b. Unusual sensations affecting either the vision, hearing, smell taste, or touch c. Memory or emotional disturbances
2. Complex (Impairment of awareness)	Automatisms such as lip smacking, chewing, fidgeting, walking and other repetitive, involuntary but coordinated movements
3. Partial seizure with secondary generalization	Symptoms that are initially associated with a preservation of consciousness that then evolves into a loss of consciousness and convulsions.

Partial seizures are divided into simple, complex and those that evolve into secondary generalized seizures. The difference between simple and complex seizures is that during simple partial seizures, patients retain awareness; during complex partial seizures, they lose awareness.

Simple partial seizures are further subdivided into four categories according to the nature of their symptoms: motor, autonomic, sensory, or psychological. Motor symptoms include movements such as jerking and stiffening. Sensory symptoms caused by seizures involve unusual sensations affecting any of the five senses (vision, hearing, smell, taste, or touch). When simple partial seizures cause sensory symptoms only (and not motor symptoms), they are called "auras."

Autonomic symptoms affect the autonomic nervous system, which is the group of nerves that control the functions of our organs, like the heart, stomach, bladder, intestines. Therefore autonomic symptoms are things like racing heart beat, stomach upset, diarrhea, loss of bladder control. The only common autonomic symptom is a peculiar sensation in the stomach that is experienced by some patients with a type of epilepsy called temporal lobe epilepsy. Simple partial seizures with psychological symptoms are characterized by various experiences involving memory (the sensation of *deja-vu*), emotions (such as fear or pleasure), or other complex psychological phenomena.

Complex partial seizures, by definition, include impairment of awareness. Patients seem to be "out of touch," "out of it," or "staring into space" during these seizures. There may also be some "complex" symptoms called automatisms. Automatisms consist of involuntary but coordinated movements that tend to be purposeless and repetitive. Common automatisms include lip smacking, chewing, fidgeting, and walking. The third kind of **partial seizure** is one that begins as a focal seizure and evolves into a generalized convulsive ("grand-mal") seizure. Most patients with partial seizures have simple partial, complex partial, and secondarily generalized seizures. In about two-thirds of patients with partial epilepsy, seizures can be controlled with medications. Partial seizures that cannot be treated with drugs can often be treated surgically[9].

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